

1           1. A method of hybridizing a first nucleic acid to  
2 a second nucleic acid at least partially complementary to  
3 the first nucleic acid, the method comprising:

4           (1) providing a sample vessel and pressure  
5 controller for the vessel; and

6           (2) contacting the first and second nucleic acids  
7 within the vessel at a pressure above ambient pressure that  
8 is effective to enhance hybridization of the first and  
9 second nucleic acids.

1           2. The method of claim 1, further providing a  
2 nucleic acid polymerase and at least one nucleotide  
3 triphosphate and wherein the first nucleic acid has a 3'  
4 terminal nucleotide that hybridizes to an internal  
5 nucleotide in the second nucleic acid, the first nucleic  
6 acid capable of being extended at least one nucleotide by  
7 the polymerase using the second nucleic acid as a template.

1           3. The method of claim 2, further comprising  
2 cycling pressure in the vessel between a first higher  
3 pressure at which the first and second nucleic acid are  
4 hybridized and a second lower pressure at which the first  
5 and second nucleic acid are denatured.

1           4. The method of claim 3, further comprising  
2 providing a temperature control for the sample vessel, and  
3 cycling the temperature between a lower temperature and a  
4 higher temperature, such that the first and second nucleic  
5 acids hybridize at the first pressure and lower temperature,  
6 and such that the first and second nucleic acids denature at  
7 the second pressure and higher temperature.

1           5.    The method of claim 3, wherein the vessel is  
2 maintained at a constant temperature as the pressure is  
3 cycled.

1           6.    The method of claim 1, further comprising  
2 washing away unhybridized nucleic acids after increasing the  
3 pressure but before decreasing the pressure.

1           7.    The method of claim 1, wherein the pressure  
2 inside the vessel is increased to greater than 10,000 psi.

1           8.    A method of detecting in a sample the presence  
2 of a nucleic acid that hybridizes to a reference nucleic  
3 acid at a first higher pressure but not at a second lower  
4 pressure, the method comprising:

5           (1) providing a sample vessel and pressure  
6 controller for the vessel; and in any order

7           (2) contacting the reference sequence with the  
8 sample in the vessel at the first pressure;

9           (3) contacting the reference sequence with the  
10 sample in the pressure vessel at the second pressure; and

11           (4) detecting the presence of a nucleic acid that  
12 hybridizes to the reference nucleic acid at the first  
13 pressure but not at the second pressure.

1           9.    The method of claim 8, wherein the reference  
2 sequence is first contacted with the sample and  
3 hybridization is detected, and then the pressure is lowered  
4 and the absence of hybridization is detected.

10. A method of discriminating between a first nucleic acid and a second nucleic acid that is different from the first nucleic acid, the method comprising,

- (1) providing a sample vessel and pressure controller for the vessel;
- (2) maintaining the vessel at a constant pressure;
- (3) providing the first and second nucleic acid and a reference nucleic acid in the vessel under conditions that do not allow either the first or the second nucleic acid to hybridize to the reference nucleic acid;
- (4) perturbing at least one condition to establish conditions that permit the first nucleic acid to form a complex with the reference nucleic acid at equilibrium and to permit the second nucleic acid to form a complex with the reference nucleic acid at equilibrium; and
- (5) comparing the time necessary to achieve equilibrium hybridization between the first nucleic acid and the reference nucleic acid with the time necessary to achieve equilibrium hybridization between the second nucleic acid and the reference nucleic acid, wherein the difference indicates the relative difference in sequence between the first and the second nucleic acids.

11. The method of claim 10, wherein the perturbation is a change in temperature inside the vessel.

12. The method of claim 10, wherein the perturbation is a change in an electric field inside the vessel.

13. The method of claim 10, wherein the sample vessel is maintained at a pressure of at least 10,000 psi.

14. A method of discriminating between a first nucleic acid and a second nucleic acid that is different from the first nucleic acid, the method comprising,

- (1) providing a sample vessel and pressure controller for the vessel;
- (2) providing the first and second nucleic acid and a reference nucleic acid in the vessel under a first pressure that does not allow either the first or the second nucleic acid to hybridize to the reference nucleic acid;
- (3) perturbing the pressure to establish conditions that permit the first nucleic acid to form a complex with the reference nucleic acid at equilibrium and to permit the second nucleic acid to form a complex with the reference nucleic acid at equilibrium; and
- (4) comparing the time necessary to achieve equilibrium hybridization between the first nucleic acid and the reference nucleic acid with the time necessary to achieve equilibrium hybridization between the second nucleic acid and the reference nucleic acid, wherein the difference indicates the relative difference in sequence between the first and the second nucleic acids.

15. The method of claim 14, wherein the sample vessel is maintained at a pressure of at least 10,000 psi.

16. The method of claim 4, wherein a portion of the second nucleic acid is amplified.